ELECTROPHYSIOLOGICAL STUDY ON THE SO-CALLED SENSITIZING EFFECT OF HALOTHANE TO CATECHOLAMINES IN THE DOG CARDIAC MUSCLE

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Summary.....The electrophysiological basis of pharmacological actions of halothane on canine cardiac fibers was examined to elucidate the mechanism of the induction of the arrhythmia by the combination of anesthetic and epinephrine. The pacemaker activity of the right bundle branch (RBB) was compared with that of the sinus node under the influence of halothane and epinephrine. In the spontaneously active fiber of RBB, halothane (1.3% v/v) caused remarkable increase in the slope of pacemaker potential and in the rate of firing in most preparations. In contrast, halothane produced a profound depression in pacemaker activity of the sinus node in half number of preparations, but the remaining preparations were not affected significantly. The positive chronotropic action of epinephrine was augmented by halothane in RBB preparations, while the enhancement was not observed in atrial preparations. These effects might result in an enhanced liability to arrhythmia.

It is well known that some hydrocarbon inhalation anesthetics enhance the arrhythmogenic action of epinephrine. Although numerous investigations have been carried out on this drug-interaction from various points of view, there is no established theory. This subject was reviewed and summarized by Katz and Epstein (1968). Many factors which contribute to the production of the arrhythmias are generally classified into two groups: intracardiac and extracardiac factors. The former factors are effects brought about both by anesthetics and by catecholamines, and the latter factors are such as arterial pressure level (Dresel and Sutter, 1961), hyperkalemia (O'Brien et al., 1953), and nervous influence (Price et al., 1963). Although the possibility of the participation of extracardiac factors cannot completely be excluded, most of the recent investigations indicate that such an arrhythmogenic situation, 'cardiac sensitization' to catecholamines, is induced by the direct cardiac action of anesthetics (Davis et al., 1969; Reynolds et al., 1970).

In the electrophysiological studies on the cardiac actions of anesthetics, several investigators recently pointed out that anesthetics had a tendency to develop arrhythmias,

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resulting from their effects on the sinus node and on Purkinje fibers. Davis et al. (1969) and Reynolds et al. (1970) found that methoxyflurane and cyclopropane enhanced the positive action of epinephrine on the slope of pacemaker potential of Purkinje fibers, while no evidence has been obtained that halothane enhances the effect of epinephrine, and, on the contrary, even an antiarrhythmic action of halothane has been reported in vivo (Logic and Morrow, 1972) and in vitro (Reynolds et al., 1970).

The present experiments were therefore carried out to explore the mechanism of the drug-interaction between halothane and epinephrine on spontaneously active fibers of canine hearts.

MATERIALS AND METHODS

For electrophysiological studies, mongrel dogs weighing from 5 to 15 kg were anesthetized with thiopental sodium (30 mg/kg, i.v.) and the heart was quickly removed. Several suitable strips were cut out from the right atrium, ventricular septum and right ventricle and stored in oxygenated Tyrode's solution. The composition of the solution in mM was ; NaCl 137.2, CaCl₂ 1.8, KCl 2.7, MgCl₂ 1.0, glucose 11.0, NaH₂PO₄ 0.4 and NaHCO₃ 12.0. Each strip was immersed in the solution of a 30 ml-tissue bath bubbled with 95% O₂ and 5% CO₂ and kept at 37°C.

The electrical activities of the cardiac fibers (sinus node, right bundle branch and Purkinje fiber) were observed with conventional microelectrode techniques. The quiescent fibers in the right ventricular preparations were electrically driven through bipolar platinum electrodes with rectangular pulses of 5 msec in duration at a frequency of 0.8 Hz.

To obtain homogeneous halothane-O₂-CO₂-mixed gas of desired composition we devised a halothane-vaporizer suitable for low flow rates (Fig. 1). The concentration of halothane used in the present study was 1.3% (v/v) which lies within the range of concentration clinically used. When the effect of halothane was examined, O₂-CO₂ gas supplied to the bath was replaced with the halothane-containing gas without changing the flow rate, and the preparation was allowed to stand for 5 min or longer to obtain the equilibrium between halothane and Tyrode's solution.

For the study of beating rate of the atrium, young dogs weighing from 4 to 8 kg were used. The dissected atrial preparations were immersed in the solution of 150 ml-tissue bath through which the gas of the composition described above was bubbled at a high flow rate. The temperature of the solution was maintained at 35-37°C. The isometric contraction and the beating rate were measured by means of a strain gauge transducer and a rate-tachometer, respectively, and were recorded on an ink-writing oscillograph (Nihonkoden Co.). Resting tension of 1 g was loaded.

Following drugs were used: halothane (Fluothane) which was the gift from Hoechst Japan Ltd., to whom the authors are very grateful, and epinephrine hydrochloride (Sankyo Co.).

Halothane-induced sensitization to catecholamine

Fig. 1. The apparatus for vaporizing and introducing halothane into the tissue bath at a constant concentration.

From the lower end of the tubing indicated by an arrow 95% O₂-5% CO₂ gas was introduced into the apparatus. Two rotameters (30 and 100 ml/min ranges) were used to adjust flow ratio. Halothane was vaporized at 0°C. The concentration of halothane was calibrated spectrophotometrically at the wave length of 240 nm.

RESULTS

Spontaneously active fibers in the canine right bundle branch (RBB).

The effect of halothane on RBB was very distinct and significant. This was reflected on the increase in the slope of pacemaker potential (SPP) and also in the rate of firing. Action potential amplitude, threshold potential (TP) and maximum diastolic potential (MDP) were reduced. These are clearly demonstrated in Fig. 2. From these results, it is conceivable that the pacemaker activity of RBB will be significantly facilitated by halothane.

To examine the interaction of halothane and epinephrine on RBB, responses to epinephrine in the presence of halothane were compared with those in the absence of halothane. Fig. 3 is a typical record of these experiments, showing that halothane and epinephrine acted synergistically resulting a prominent increase in the firing rate. These results were obtained in 8 of 12 dogs. In some preparations bigeminal rhythm or premature beats were observed by the combination of halothane and epinephrine.

Quiescent Purkinje fibers of the right ventricular wall.

Halothane affected the repolarization phase of action potential. Fig. 4 shows that main effects of halothane were an increase in the slope of the phase 2 and a decrease in the slope of the phase 3. The time to repolarize to -60 mV, which is an approximate measure of the functional refractory period (Weidmann, 1955; Temte et al., 1967) was decreased, while the time to 90% repolarization remained unchanged. These results are

Fig. 2. Electrophysiological effect of halothane on a spontaneously active fiber in RBB. A: Normal membrane activity; B and C: after the exposure to halothane for 5 and 15 min, respectively. D and E are rapid tracings of A and C. Horizontal lines and spots on them represent the zero potential level and 200 msec intervals, respectively. Voltage calibration applies to all panels.

Fig. 3. The interaction of halothane and epinephrine on a spontaneously active fiber in RBB. The upper and the lower records were obtained from separate experiments. A and D: Normal membrane activity; B: after the exposure to halothane for 15 min; C: 30 sec after the addition of epinephrine following B; E: 30 sec after the addition of epinephrine following D, in the absence of halotane. Other explanations are as indicated in Fig. 2.

in agreement with those obtained by Hauswirth (1969) and Reynolds et al. (1970). Halothane exerted no recognizable influence on the maximum rate of rise in the present investigations.

Sinus node.

In 3 out of 6 experiments, halothane showed a profound depressing action on spon-

Halothane-induced sensitization to catecholamine

Fig. 4. The interaction of halothane and epinephrine on a Purkinje fiber driven electrically. 1: Normal; 2: after the exposure to halothane for 20 min; 3: 30 sec after the addition of epinephrine following 2; 4: 1 and 2 are superimposed. The time to repolarize to -60 mV of the record 1, 2 and 3 was 391, 336 and 366 msec, respectively. Other explanations are as indicated in Fig. 2.

Fig. 5. Electrophysiologic effect of halothane on the sinus node. The time in min after the start of exposure to halothane is indicated under each panel. Other explanations are as indicated in Fig. 2.

taneously active fibers of the sinus, while the other strips were unaffected. Fig. 5 is a typical record of the depressing effect. Until 20 min after introducing halothane into the bath, the electrical parameters of the sinus node was not altered except for a slight increase in the duration of action potential and a slight decrease in the rate of firing (Fig. 5, pper

Fig. 6. Dose-response curve for epinephrine in the presence and absence of halothane (1.3%) in spontaneously active atrial preparations. —○—, In the absence of halothane. An open circle, C, indicates control value. —●—, In the presence of halothane. Two closed circles, h1 and h2, indicate the values before and after the introduction of halothane, respectively. Each point is a mean of five values, and vertical bars represent standard errors.

right). After about 20 min, action potentials were abruptly abolished, and possibly non-propagating potentials of about 24 mV in amplitude remained.

In separate pharmacodynamic experiments, the combined effect of halothane and epinephrine on the beating rate of atria was examined. Before the experiment the preparations were allowed to stand for at least 1 hr. Fifteen minutes after the start of introducing halothane into the bath, epinephrine was given cumulatively. The dose-response curve for positive chronotropic action of epinephrine is shown in Fig. 6. No statistical difference was found between the dose-response curves, but halothane tended to reduce the effect of the lower doses of epinephrine, and to enhance the effect of the highest dose of epinephrine. Similar results were obtained also in a lower concentration of halothane of 0.6%. Corresponding to the results obtained in the present electrophysiological studies, spontaneous contractions were often abolished by introducing halothane. Such cases were excluded from the data. From this reason the calculated mean beating rate was not decreased by halothane. The contractile force was decreased to $45.6 \pm 3.4\%$ ($n=5$) 15 min after the introduction of halothane.

DISCUSSION

Although continuous arrhythmias could not be induced by the combination of halothane and epinephrine in isolated preparations used in the present studies, cardiac specialized fibers seemed to become prone to suffer from arrhythmias by halothane alone.

It was observed that halothane had facilitating actions on RBB cells, resulting from an increase in SPP and a decrease in MDP, although a decrease in TP affected the cells in the opposite direction. As regards other cardio-sensitizing anesthetics, methoxyflurane

and cyclopropane, similar effects have been reported in Purkinje fibers (Davis et al., 1969 ; Reynolds et al., 1967). These facilitating actions suggest a possibility of generating a heterotropic spontaneous impulse in the bundle branch. In fact incidences of significant arrhythmias have been observed clinically during anesthesia irrespective of the use of epinephrine: a wandering pacemaker and premature ventricular systoles (Kuner et al., 1967).

Although the present results are contradictory to those obtained by Reynolds et al. (1970), who showed that halothane slowed the pacemaker activity of Purkinje fibers and that it diminished the facilitating action of epinephrine, the disagreement might possibly be due to the difference in preparations (RBB in the present studies and terminal Purkinje fibers in his studies), and also in halothane concentration (1.3% in the present studies and 2.5% in his studies).

In the present investigations repolarization phase of action potentials of quiescent Purkinje fibers was affected by halothane resulting in a change in contour of action potential which may suggest a shortening of functional refractory period. These results were in agreement with those of Hauswirth (1969) and Reynolds et al. (1970).

In the present studies it was observed that halothane decreased the firing rate of atrial pacemaker cells. Although it was not clear whether the penetrated cell was the true pacemaker cell or a neighboring cell, these results indicate a profound depression of pacemaker activity of the sinus node by halothane. These results are in agreement with those of Hauswirth and Schaer (1967) who used rabbit atria. Halothane did not significantly influence the positive chronotropic effect of epinephrine in the atrium preparation, although it tended to enhance the effect of the highest dose of epinephrine, $10^{-5}M$, and also tended to depress the effect of lower doses of epinephrine.

In turn, Hashimoto and Hashimoto (1972) have proposed as the mechanism of halothane-induced sensitization of the ventricle to epinephrine, which results in minor ventricular arrhythmias, that the activity of ventricle exceeds that of the sinus node resulting mainly from the slowing of sinus node activity by halothane, rather than from the accelerated activity of the ventricle by halothane and epinephrine. Although changes in the function of the whole heart should carefully be deduced from such results as those obtained in the present investigations in which separate preparations of each part of the whole heart were used, it seems reasonable to consider that not only the decrease in sinus node activity, but also an increase in the liability of ventricular specialized fibers to cause arrhythmias after the combined application of halothane and epinephrine may play an important role.

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